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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/353,423	07/15/1999	TATTANAHALLI L. NAGABHUSHAN	CJ-0776QK	3515

7590 11/03/2005

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/353,423	NAGABHUSHAN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,26-29 and 40-42* is/are pending in the application.

4a) Of the above claim(s) *40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 15, 2005 (hereinafter referred to as "the response") has been entered. Claims 19 and 26 have been amended. Claims 1, 25, 30-34, and 36-39 have been cancelled. Claims 40-42 have been newly added.

Accordingly, Claims 19-24, 26-29, and 40-42 are pending in the instant application.

Election by Original Presentation

Newly submitted Claims 40-42 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly added claims are directed to a mammalian cell which is patentably distinct from the originally presented invention. The originally presented invention is directed to (i) a method for providing a patient with an interferon α (IFNα) polypeptide, (ii) a method for increasing interferon α levels in a patient, (iii) a recombinant vector encoding an IFNα polypeptide, and (iv) a method of treating hepatocellular carcinoma in a mammal. The newly submitted invention is unrelated to the invention originally presented. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed as being used together. The mammalian cells, as claimed, are not used in the methods of the inventions under examination, which are directed to methods of using a recombinant vector.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, Claims 40-42 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP §821.03.

Claims 19-24 and 26-29 are examined herein.

The rejection of Claim19 under 35 U.S.C. 102(a) is withdrawn in view of the amendment to the claim.

The rejections of Claims 1, 25, 30-34, and 36-39 are withdrawn in view of the cancellation of these claims.

Claim Objections

Claims 28 and 29 are objected to for depending upon cancelled claim 25.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-24 and 26-29 stand rejected and Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,069,133 (Chiou et al., priority to March 1996), Rutherford et al. (July 1996, J. of Interferon and Cytokine Research 16(7): 507-510), and Zhang et al. (April 1996, PNAS 93: 4513-4518), for reasons of record advanced in the Office Action of 2/10/05.

At page 6, paragraph 2 of the response, Applicants assert that Rutherford used a cell line that has the IFN gene chromosomally integrated. Applicants point to the Coulombe reference for teaching the plasmid vector that was used in the Rutherford reference. Applicants state that "[o]bviously the plasmid

vectors created by Coulombe were designed to effect the chromosomal integration of Coulombe's highly derived IFN gene." First, in response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller* 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.* 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the Office action of 2/10/05, the Rutherford et al. reference is cited for disclosing "a recombinant vector for expressing an interferon-α polypeptide in a mammalian cell, wherein the nucleic acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence" and further for disclosing that "the intracellular expression of interferon-α renders the cells less susceptible to encephalomyocarditis (EMC) virus infection." The rejection further states

> Since Rutherford et al. disclose the antiviral activity of intracellular interferon and Zhang et al. disclose using an adenovirus to deliver the interferon gene to cells *in vivo*, one of skill in the art would have been motivated to prepare adenoviral vectors comprising an interferon-α gene lacking the secretion leader sequence so that the vectors could be used for *in vivo* delivery of the gene which would then drive expression of intracellular interferon-α in cells. Since Chiou et al. disclose that interferon-α, and particularly IFN-α2b, are useful for their antiviral activity and are particularly useful for delivery to liver cells for the treatment of HBV, one of skill in the art would have been motivated to use a liver-specific promoter to drive expression of an intracellular form of IFNα, particularly IFN-α2b, in the liver to test its antiviral activity against HBV. (page 9, paragraph 4).

Thus, sufficient motivation for making **adenoviral vectors** that encode a **non-secreted form of IFNα** is provided. The fact that Rutherford et al. used a cell line having a chromosomally integrated IFNα gene for their *in vitro* studies, does not pertain to the instant grounds of rejection, because one of skill in the art readily recognizes that a variety of means for transfecting cells are available in the art and while cell lines that stably express a transfected gene are preferred for *in vitro* studies, adenoviral vectors are typically the vector of choice for *in vivo* gene delivery. Thus, Rutherford et al. is cited for teaching an advantageous property of non-secreted IFNα, i.e. its intracellular anti-viral activity, but **Zhang et al.** is cited for teaching the *in vivo* administration of an **adenovirus** comprising the human consensus IFN gene.

At page 6, paragraph 3 of the response, Applicants assert that Coulombe made many significant modifications to the IFNα gene encoded by their plasmid. Suffice it to say that independent Claim 19 recites "a nucleic acid segment encoding an interferon-α polypeptide ... wherein the nucleic acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence" and therefore covers an adenoviral vector encoding **any non-secreted form of interferon-α.** Therefore, the interferon-α gene of Rutherford's plasmid would be included in Claim 19 as instantly claimed. Thus, Applicants are arguing limitations not in the claims. Furthermore, it is noted that the vector of Rutherford et al., despite a few modifications to the IFNα gene, encodes the **same** protein product as its natural counterpart (see Coulombe et al. (1986), abstract, for description of the recombinant interferon gene).

At page 6, paragraph 4 of the response, Applicants assert that "[n]othing in Coulombe suggests that episomal *adenoviral* vectors encoding non-secreted human consensus sequence IFN genes would be useful for changing the properties of transformed cells." First, Applicants are reminded that the rejection is based on Rutherford et al. (in combination with Zhang et al. and Chiou et al.), not Coulombe. Rutherford's title is "Expression of Intracellular Interferon Constitutively Activates ISGF3 and Confers Resistance to EMC Viral Infection." Thus, the antiviral properties of intracellular interferon readily suggests that such genes are highly "useful for changing the properties of transformed cells," contrary to Applicants' assertion. Second, Applicants are again reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller* 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.* 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of the 3 references that suggests that **adenoviral** vectors encoding non-secreted forms of interferon-α would be useful. **Zhang et al.** is cited for disclosing the *in vivo* administration of an **adenovirus** comprising the human consensus IFN gene.

At page 7, paragraph 2 of the response, Applicants suggest that Rutherford's 1996 report of an approximately 2-fold increase in virus resistance in cells carrying low copy numbers of the integrated

IFNα gene is somehow at odds with Coulombe's 1986 report. No support is offered for this assertion. The experiments performed by Rutherford et al. (1996) were **not** performed by Coulombe et al. (1986).

At page 7, paragraph 3 of the response, Applicants assert that Rutherford teaches away from the creation of episomally-replicating adenoviral vectors comprising a non-secreted human IFNα "lacking artificial introns." Applicants are again arguing limitations that are not in the claims. There is no such recitation in the claims limiting the IFNα-encoding nucleic acid segment to one that is "lacking artificial introns."

In the paragraph bridging pages 7-8 of the response, Applicants dismiss the other two references relied upon for the rejection because neither individually teaches the claimed invention. First, Applicants assert that Chiou et al. does not teach intracellular IFNα, nor does it teach an adenoviral vector encoding IFNα. Nevertheless, Chiou et al. is not cited for such teachings, but rather is cited for teaching the antiviral properties of IFNα, particularly IFN-α2b, and particularly for its antiviral activity against HBV and HCV infections. Thus, Chiou et al. teaches the desirability of delivering IFNα to the liver. Second, Applicants assert that Zhang et al., although disclosing adenoviral vectors comprising the human consensus IFN gene, does not disclose "adenoviral vectors which encode a *non-secreted* IFN gene." However, Zhang et al. is not cited under 35 U.S.C. 102, but rather is cited as one of a combination of references that renders the claimed invention obvious. Thus, Zhang et al. need not disclose "adenoviral vectors which encode a *non-secreted* IFN gene" as Applicants suggest, because Zhang et al. **in combination with** Rutherford et al. and Chiou et al. renders the claimed vector obvious. Again, Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller* 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.* 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of the 3 references that suggests that **adenoviral** vectors encoding **non-secreted** forms of interferon-α would be useful and therefore obvious.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history

information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER